REMARKS

Claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68 and 71-76 were previously pending and are still pending and under examination in this application. Claims 1, 11 and 71-74 have been amended. No new matter has been added.

Rejections Under 35 U.S.C. §112

The Examiner maintained the rejection of claims 1, 6, 11, 16, and 71-74 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner concedes that the specification provides support for "a" diabetic complication but maintains that there is no support in the specification for the phrase "one or more" diabetic complications.

Without conceding the correctness of the Examiner's position and in order to advance prosecution, Applicant has amended claims 1, 11 and 71-74 to overcome this rejection. Claim 6 depends from claim 1 and claim 16 depends from claim 11. Support for the claim amendments may be found in the application as filed.

In view of the above arguments and amendments, withdrawal of the claim rejections under 35 U.S.C. 112, first paragraph is kindly requested.

Rejections Under 35 U.S.C. §103

The Examiner maintained the rejection of claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as obvious in view Rodriguez-Moran et al. (Journal of Diabetes and Its Complications 13;4:211-215, 1999). The Examiner states that Rodriguez-Moran teaches that elevated serum CRP levels have been found in type II diabetics and in diabetics with foot ulcers and that elevated serum CRP levels are also found in noncontrolled type II diabetic patients. The Examiner asserts that "[w]hile the reference does not specifically teach characterizing a risk profile for developing diabetes or evaluating the likelihood that an individual will benefit from treatment, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made [to] measure serum CRP levels for said uses given CRP's known association with type II diabetes, i.e., it is obvious to measure a known marker for the presence of, or predisposition to a disease."

The Examiner considered Applicant's arguments filed on November 29, 2006 but did not find them persuasive. According to the Examiner, Rodriguez-Moran renders the claimed methods obvious. The Examiner alleges that "given the often asymptomatic nature ("apparently healthy") of diabetes, the testing for known markers of the disease would have been obvious to the ordinarily skilled artisan". The Examiner asserts that the point of the Applicant's argument that Rodriguez-Moran teaches that elevated CRP is more likely the result rather than the cause of the diabetic condition was unclear to the Examiner. According to the Examiner, "the cause of the elevated CRP is irrelevant – elevated CRP is simply a marker for type II diabetes. The reference teaches that noncontrolled type II diabetics display high CRP levels and as set forth above, it is well-established that many "apparently healthy" individuals actually suffer from type II diabetes, i.e. the individuals have noncontrolled diabetes."

Applicant respectfully traverses the rejection. The instant claims are directed at evaluating individuals who do not yet have diabetes and making assessments based on those evaluations. The invention *predicts* the risk of a *future* disorder (diabetes or diabetic complication) *prospectively* (i.e., before the diabetic disorder happens) among individuals without current evidence of disease (i.e., *"apparently healthy"* individuals) based on a level of C-reactive protein (CRP).

As currently pending, claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 are not obvious over Rodriguez-Moran because Rodriguez-Moran does not and could not address whether the level of CRP is *predictive* of a *future* diabetes or diabetic complications in *apparently healthy* individuals. Rodriguez-Moran did not evaluate individuals who were apparently healthy (i.e., without diabetes). Instead, Rodriguez-Moran compared the serum levels of CRP in patients with type II diabetes (i.e., after the diabetic disorder happened). Rodriguez-Moran found that patients with type II diabetes have higher levels of CRP compared to healthy controls. Patients with type II diabetes are <u>not</u> apparently healthy and data from such a group cannot be used to make conclusions regarding apparently healthy individuals.

The Examiner argues that "many "apparently healthy" individuals actually suffer from type II diabetes, i.e. the individuals have noncontrolled diabetes". Applicant submits that individuals with noncontrolled diabetes are not apparently healthy. Apparently healthy individuals as defined in the specification on page 9, lines 4-7 are individuals who if examined by a medical professional would be characterized as healthy and free of symptoms of disease.

When individuals with noncontrolled diabetes are examined by a medical professional they will not be characterized as healthy and free of symptoms of disease. Instead, such individuals will be characterized as diabetic and will likely be treated.

Furthermore, Rodriguez-Moran teaches that type II diabetes patients had significantly higher serum levels of CRP. Rodriguez-Moran compared the serum levels of CRP in type II diabetic patients retrospectively (i.e., after the diabetic disorder happened). Rodriguez-Moran is incapable of providing a basis for one of ordinary skill in the art to conclude that elevated CRP is a risk factor for developing future diabetes. The Rodriguez-Moran study only shows that patients with type II diabetes have elevated CRP levels. This is not proof that elevated CRP levels predict future diabetes. Based on the study of Rodriguez-Moran one of ordinary skill in the art would have known that it is impossible to distinguish whether the elevated CRP levels simply result from the existing diabetic condition, or whether elevated CRP levels are predictive of diabetes because the CRP levels were measured after the diabetic disorder happened. In fact, the teachings of Rodriguez-Moran suggest that elevated CRP (a known marker of inflammation) might probably be the result of the diabetic condition rather than the cause of the diabetes (see Rodriguez-Moran et al. p. 215 right-hand column):

> "A probable involved pathway could be related to the raising of serum viscosity and shear stress associated to hyperglycemia, producing endothelium dysfunction and inflammation and in this way, increasing citokines release and thus elevating CRP levels."

Thus, Rodriguez-Moran does not address whether the level of CRP is *predictive* of *future* diabetes in individuals because if the elevation in the levels of CRP is the result of or is caused by the diabetes, the elevated levels of CRP cannot predict future diabetes (i.e., cannot predict diabetes before it happens).

In summary, Rodriguez-Moran is incapable of providing a basis for one of ordinary skill in the art to conclude that elevated CRP is a risk factor for developing diabetes in the future. Accordingly, the teachings of Rodriguez-Moran do not render the claimed methods obvious.

In view of the above arguments, withdrawal of the rejection of claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as obvious in view of Rodriguez-Moran et al. is respectfully requested.

The Examiner maintained the rejection of claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as obvious in view of Schalkwijk et al. (Diabetologica (1999) 42:351-357). The Examiner states that Schalkwijk teaches that elevated serum CRP levels have been found in type I diabetes particularly referring to the Results on page 211 and to table 2. The Examiner asserts that "[w]hile the reference does not specifically teach characterizing a risk profile for developing diabetes or evaluating the likelihood that an individual will benefit from treatment, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made [to] measure serum CRP levels for said uses given CRP's known association with type I diabetes, i.e., it is obvious to measure a known marker for the presence of, or predisposition to a disease."

Applicant respectfully traverses the rejection. The arguments presented above in response to the rejection of the claims as obvious in view Rodriguez-Moran are reiterated here. As stated above, the instant claims all are directed at evaluating individuals who do not yet have diabetes and making assessments based on those evaluations.

Schalkwijk does not, and could not, address whether a level of CRP is predictive of developing diabetes or diabetic complications or whether an apparently healthy individual (i.e., without diabetes) would benefit from prophylactic treatment to prevent diabetes or diabetic complications. Schalkwijk did not evaluate individuals who were apparently healthy (i.e., without diabetes). Instead, Schalkwijk compared the serum levels of CRP in type I diabetic patients (i.e., after the diabetic disorder happened). Schalkwijk teaches that patients with type I diabetes had higher serum levels of CRP. It should be noted that the study of Schalkwijk was not designed in a manner that would permit one to conclude that elevated levels of CRP predict diabetes. The Schalkwijk study only shows that patients with diabetes have elevated CRP levels. This is not proof that elevated CRP levels predict future diabetes. Based on the data in Schalkwijk, one of ordinary skill in the art would have known that it is impossible to conclude definitively that the elevated CRP levels simply result from the existing diabetic condition, or whether elevated CRP levels are predictive of diabetes because the CRP levels were measured after the diabetic disorder happened. In fact, the teachings of Schalkwijk suggest that elevated CRP is more likely the result of the diabetic condition rather than the cause of the diabetes (see Schalkwijk p. 356):

> "Various possible mechanisms could induce chronic low degree inflammation in diabetes, including activation of macrophages, increased oxidative stress or an induction of cytokines. One of the pathophysiological consequences of hyperglycaemia is the phenomenon of nonenzymatic glycation and the formation of advanced glycation end products (AGEs). AGEs have been shown to activate macrophages, to increase oxidative stress and to induce, in macrophages, the synthesis of interleukin-1 and tumor necrosis factor-α and, in vivo in mice, the expression of interleukin-6 mRNA. Many of the possible mechanisms leading to chronic low degree inflammation could be related to nonenzymatic glycation. Another possibility is that increases in CRP are related to adipose-tissue-derived cytokines." (Citations omitted)

Thus, Schalkwijk does not address whether the level of CRP is *predictive* of diabetes in *apparently healthy* individuals because if the elevation in the levels of CRP is the result of or is caused by the diabetes, the elevated levels of CRP cannot predict future diabetes (i.e., cannot predict diabetes before it happens). Therefore, Schalkwijk is incapable of providing a basis for one of ordinary skill in the art to conclude that elevated CRP is a risk factor for developing diabetes in the future. Accordingly, the teachings of Schalkwijk do not render the claimed methods obvious.

In view of the above arguments, withdrawal of the rejection of claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as obvious in view of Schalkwijk is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Ridker et al., Applicant

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